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## RESEARCH ARTICLE

# Oxidation of Alcohols and Aldehydes with Peracetic Acid and a Mn(II)/Pyridin-2-Carboxylate Catalyst: Substrate and Continuous Flow Studies

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**Abstract:** A homogeneous catalyst system, consisting of Mn(OAc)<sub>2</sub> and 2-picolinic acid was studied for alcohol oxidation using peracetic acid as the oxidant. Catalyst loadings as low as 0.01 mol% could be utilized and the system compared well to other peroxide based methods. The utilization of continuous flow allowed the fast, exothermic reactions to be carried out in a safe and scalable manner.

## Introduction

Carbonyl compounds are very important in the pharmaceutical and fine chemical industries, with ketones, aldehydes and carboxylic acids all used as both chemical intermediates and supplied as final products. The oxidation of an alcohol is an important route for the preparation of carbonyl compounds, but this fundamental reaction is one which poses a challenge for larger scale industrial applications, such as the production of active pharmaceutical ingredients (APIs).<sup>[1]</sup> There is a need to avoid traditional stoichiometric reagents and develop catalytic methods which use sustainable oxidants such as O<sub>2</sub> and H<sub>2</sub>O<sub>2</sub>. In the last few decades, significant efforts have been made in this area but there are still challenges, with all methods having some limitations and drawbacks. Dioxygen is the most sustainable oxidant, and while heterogeneous catalysts would be ideal, so far they tend to have limited substrate scope.<sup>[2, 3]</sup> Homogeneous Pd(II) complexes have been well examined for aerobic catalysis, but the systems tend to require high catalyst loadings and often show intolerance to important functional groups.<sup>[4-7]</sup> In addition, regulations require that 2<sup>nd</sup> and 3<sup>rd</sup> row transition metals such as Pd are only present in APIs at very low concentrations, and significant efforts are often required to remove metal species.<sup>[8]</sup> Utilizing more abundant, less toxic, first-row transition metals is desirable but their behavior is quite different from 2<sup>nd</sup> and 3<sup>rd</sup> row metals, with a propensity for one-electron steps. The combination of copper complexes with TEMPO (2,2,6,6-tetramethylpiperidine 1-oxyl) allows for the two-electron oxidation of alcohols to their

corresponding aldehydes.<sup>[9, 10]</sup> These systems have excellent functional group tolerance and studies have shown they have the potential to be implemented on larger scales for the preparation of APIs.<sup>[11, 12]</sup> Nonetheless, this system is selective for the oxidation of primary alcohols to aldehydes and the oxidation of secondary alcohols to ketones requires more expensive, sterically unhindered nitroxyl co-catalysts.<sup>[13, 14]</sup> In comparison to O<sub>2</sub>, it is easier to develop first row transition metal complexes with peroxides. There are numerous reports of Mn complexes which use H<sub>2</sub>O<sub>2</sub> or *tert*-butyl hydroperoxide (TBHP) as the oxidant.<sup>[15-25]</sup> with Mobin and co-workers reviewing the topic of alcohol oxidation with manganese-based catalysts in 2020.<sup>[26]</sup> Molecular Mn complexes have been studied for a number of other important oxidation reactions, including alkene epoxidation<sup>[27]</sup> and C-H oxidation.<sup>[28]</sup> In most cases, additives are required in order to activate H<sub>2</sub>O<sub>2</sub> or generate another oxidant *in-situ*. Carboxylic acids are common additives and peracetic acid has also been shown to be a suitable oxidant. Peracetic acid (PAA) is sometimes found to be a more effective oxidant than H<sub>2</sub>O<sub>2</sub>. Indeed, Stack and co-workers studied a range of manganese complexes for alkene epoxidation and PAA was shown to be a superior oxidant to H<sub>2</sub>O<sub>2</sub>.<sup>[29-33]</sup> In their 2016 report, they utilized a simple Mn(II)/2-picolinic acid catalyst system for the epoxidation of a variety of alkenes.<sup>[33]</sup> It is also worth highlighting the studies by Browne and co-workers, who first developed the use of Mn(II)/2-picolinic acid for catalytic oxidation reactions with peroxides.<sup>[34-36]</sup> Although the focus was on H<sub>2</sub>O<sub>2</sub> and butanedione as the oxidant, they had also demonstrated that Mn(II) / 2-picolinic acid was an excellent catalyst for the epoxidation of alkenes when be combined with PAA.<sup>[36]</sup> This study also demonstrated that for this catalyst, PAA was a superior oxidant in comparison to H<sub>2</sub>O<sub>2</sub> with added acetic acid. In 2013, the Mn(II)/2-picolinic acid catalyst with H<sub>2</sub>O<sub>2</sub> and butanedione oxidant system was studied for the oxidation of aliphatic C-H groups and alcohols (primarily secondary).<sup>[23]</sup>

Comparing the epoxidation studies with Mn(II)/picolinic acid, there were some differences between using PAA versus

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H<sub>2</sub>O<sub>2</sub>/butanedione.<sup>[33, 36]</sup> As Mn(II)/2-picolinic acid had not been studied for alcohol and aldehyde oxidation with PAA, we were interested in exploring this area.

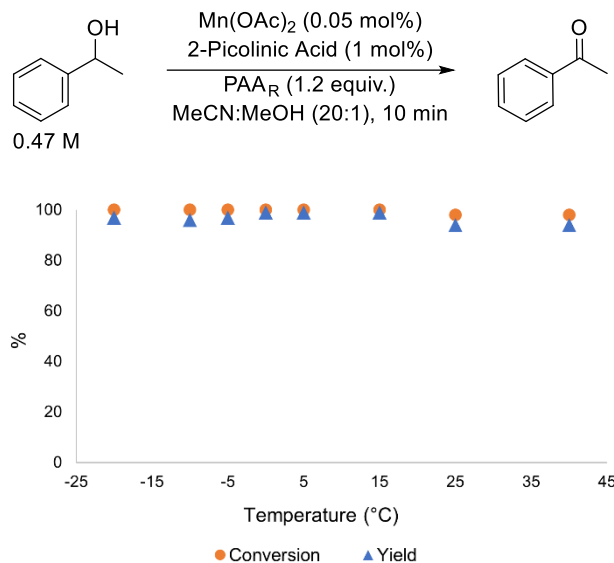
We had previously studied Mn(II)/2-picolinic acid with PAA for epoxidation reactions.<sup>[41]</sup> We were attracted to the use of PAA as an oxidant as it is a viable oxidant for larger scale applications due to its low-cost and sustainable credentials, given that it breaks down to acetic acid, oxygen and water. This is exemplified by its use in processes such as waste-water treatment.<sup>[38, 42-44]</sup>

In our studies, we modified the Mn(II)/2-picolinic acid system, further lowering the catalyst loadings and demonstrating that it was possible to operate under continuous flow conditions. Continuous flow systems are highly desirable, offering a safer and more scalable route for implementing oxidation reactions.<sup>[45-47]</sup> In this case, the interest in developing a flow system was driven by the desire to facilitate the production of PAA *in situ*,<sup>[48]</sup> and to enable better heat management for a reaction that is exothermic.<sup>[41]</sup> The focus of those studies was on epoxidation and if alcohol oxidation reactions are similarly fast, then continuous flow operation would also be the best approach if these reactions were to be scaled. Herein, we will discuss the use Mn(II)/2-picolinic acid with PAA for alcohol oxidation under both batch and flow conditions.

## Results and Discussion

### Secondary Alcohol Oxidation

Initial studies examined the oxidation of 1-phenylethanol, using conditions previously used for the oxidation of alkenes to epoxides, using 0.05 mol% of Mn(OAc)<sub>2</sub> and 1 mol% 2-picolinic acid ligand.<sup>[41]</sup> PAA was synthesized by a solid acid catalyst resin (denoted PAA<sub>R</sub>),<sup>[30, 31]</sup> and it was found that reactions only required a small excess, with close to full conversion of the alcohol with 1.2 equivalents of PAA<sub>R</sub> (Figure S1). It is known that PAA can oxidize some substrates without a catalyst, but control experiments demonstrated that no reaction occurred in the absence of metal, ligand, or oxidant on this time scale (Table S1). Examination of the reaction at various temperatures found that close to quantitative yield of acetophenone was obtained at temperatures of -20 to 40 °C (Figure 1).

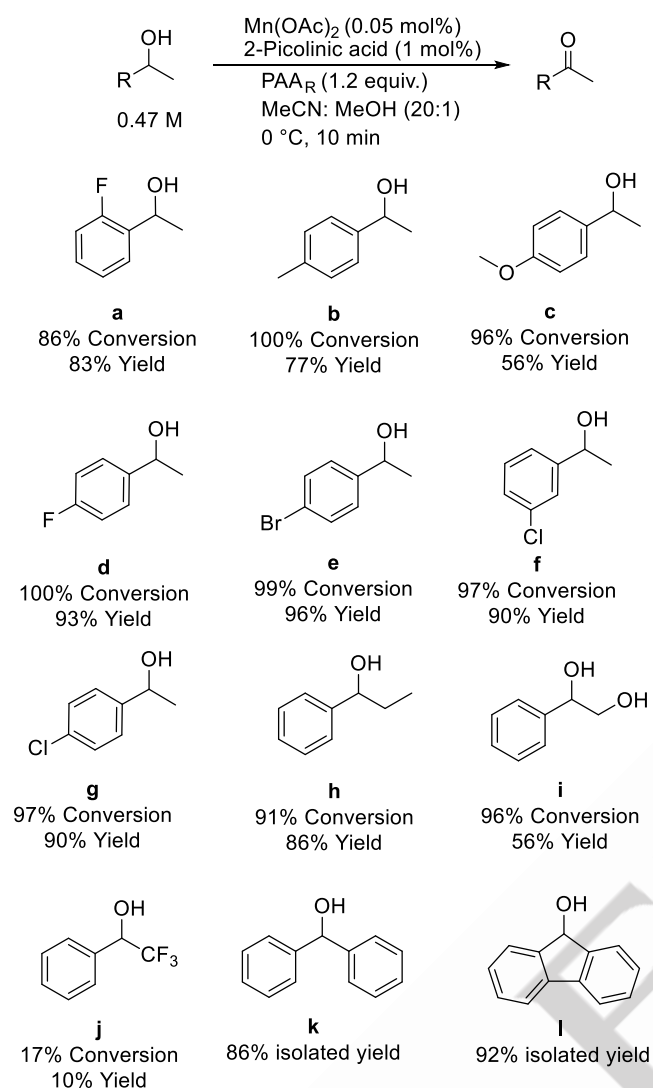


**Figure 1.** Temperature screen for the oxidation of 1-phenylethanol. Conversion and yield determined using GC-FID, with benzonitrile as an internal standard.

The reaction was exceptionally fast, reaching completion in under 1 min, even at -20 °C (Figure S2). In previous studies on using this catalyst system for epoxidation, reactions were similarly fast, with calorimetric studies indicating that scale up of the reactions would require stringent heat management in order to prevent uncontrolled temperature rise and the risk of a runaway reaction.<sup>[41]</sup> Continuous flow processes are often implemented for scale up of highly exothermic reactions of this type.

The ligand to manganese ratio was previously found to be a critical factor when transferring the alkene epoxidation reaction from batch to flow.<sup>[41]</sup> The impact of ligand to manganese ratio in secondary alcohol oxidation was investigated with the results shown in Table S2. At Mn(II) loadings of 0.05 mol% and higher, with gradual addition of peracetic acid to a stirred reaction mixture, there was little variation in conversion. Even at 0.01 mol% Mn(OAc)<sub>2</sub> and 0.2 mol% picolinic acid (Table S2, Entry 6), a yield of 86% could be obtained. The use of a 20:1 ligand:Mn ratio demonstrated better tolerance for the increased PAA concentration when PAA was added in 1 aliquot to an unstirred reaction mix (Table S2, Entry 7 vs 8). The use Mn(OTf)<sub>2</sub> delivered similar performance to the less expensive Mn(OAc)<sub>2</sub> (Table S2, Entry 2 vs 9). It was also found that ethyl acetate could be used instead of acetonitrile with no change in product yield (Table S2, Entry 10) which allows flexibility in future process design. The final conditions chosen for secondary alcohol oxidation are shown in Figure 2, which details the yields for several benzylic substrates.

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**Figure 2.** Oxidation of secondary benzylic alcohols

Substrates **a** – **j**: 1 mmol scale, 1 mL 2-picolinic acid (10 mM in MeCN), 0.1 mL Mn(OAc)<sub>2</sub> (5 mM in MeOH), 1 mL MeCN, 1.2 equiv PAA<sub>R</sub> added in 10 aliquots at 0 °C. GC-FID yield using benzonitrile internal standard. For substrate **i**, the yield refers to  $\alpha$ -hydroxy ketone product. Substrates **k** and **l**: 5 mmol scale, 5 mL 2-picolinic acid (10 mM in MeCN), 0.5 mL Mn(OAc)<sub>2</sub> (5 mM in MeOH), 5 mL MeCN, 1.2 equiv PAA<sub>R</sub> added in 10 aliquots at 0 °C.

Under these conditions, several secondary benzylic alcohol substrates were converted to their corresponding ketones in good to excellent yields. Substrates with halogen substituents on the aromatic ring (Figure 2, **a**, **d**, **e**, **f**, and **g**) were converted to their corresponding ketone in high yields with high selectivity. In the case of electron-donating substituents (**b**, and **c**), while full conversion of the alcohol substrate was observed, there was reduced ketone selectivity. The GC-FID analysis of the reaction didn't indicate significant quantities of by-products. However, GC-MS analysis was carried out to gain understanding of what other products may be formed with these substrates, with some suggested structures shown in Figure S3. It is possible the increased electron density of the aromatic ring in these substrates leads to competing ring hydroxylation.<sup>[49]</sup> In the case of the 4-

methyl derivative (**b**), C-H oxidation could also occur.<sup>[37]</sup> As a control, to test if the ketone products of these substrates are likely to undergo further reaction under the reaction conditions, 4-methyl acetophenone and 4-methoxy acetophenone were subjected to the reaction conditions. 4-Methyl acetophenone underwent 11% conversion, while 4-methoxyacetophenone underwent 38% conversion, indicating that these products will undergo further reaction leading to the lower yields.

The developed system was tested against 1-phenyl-2,2,2-trifluoroethanol as it is known that this class of alcohols are particularly difficult to oxidize; unfortunately, as can be seen in Figure 2, substrate **j**, poor reactivity was observed for this substrate.<sup>[50]</sup>

1-Phenylethane 1,2 diol (Figure 2, substrate **i**) underwent full conversion, however the  $\alpha$ -hydroxy ketone product was only formed in 56% yield. Benzoic acid and phenylacetic acid are also formed under these conditions, and these were observed by GC-MS (Figure S4). The C-C bond cleavage product, benzoic acid, has been previously reported under similar conditions for the oxidation of diols.<sup>[51]</sup> GC-MS indicated a wide range of products, many resulting from cleavage products (benzaldehyde, benzoic acid), over-oxidation (ketoester,  $\alpha$ -hydroxyester) or acetate formation due to the reaction of alcohol with acetic acid, as shown in Figure S4.

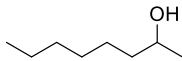
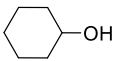
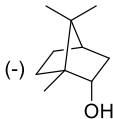
Aliphatic substrates were also tested (Table 1); these are known to be more challenging with lower reactivity generally observed.<sup>[16, 17, 22, 52, 53]</sup> The presence of oxidatively sensitive C-H bonds can also lead to selectivity issues. When the standard conditions, with 1.2 equiv. of peracetic acid were used, 2-octanol was converted to 2-octanone, but only 48% substrate conversion was observed within 10 minutes. Using a higher catalyst loading of 0.1 mol% and 1.8 equiv. of peracetic acid led to greater conversion, and selectivity decreased slightly from 83% to 76%. Similar reactivity and selectivity were observed for cyclohexanol. (–)-Borneol (Table 1, Entry 4) demonstrated good conversion with excellent selectivity to the desired camphor product.

In the case of 2-octanol (Table 1), GC-MS analysis suggested the formation of dione products (Figure S5). These dione products are most likely due to C-H oxidation occurring along the carbon chain, as this system has previously been shown to be capable of C-H oxidation.<sup>[37]</sup> To investigate if the lower selectivity was due to over-oxidation of the ketone products, the ketone products were tested under reaction conditions. 15% conversion of 2-octanone and 11% conversion of cyclohexanone was observed, indicating that over-oxidation of the ketone product contributes to the lower mass-balance due to the formation of side-products. Peracids such as peracetic acid are known to react with aldehydes and ketones to give their respective esters in a Baeyer-Villiger reaction.<sup>[54]</sup> To investigate if these competing reactions were a contributing factor in the lower mass balance observed for 2-octanol and cyclohexanol, the reaction mixtures were spiked with the hexyl acetate and caprolactone ester products respectively. In both cases, the reaction mixture trace (pre-spiked) did not show a GC peak corresponding to the Baeyer-Villiger ester product, indicating that the Baeyer-Villiger reaction did not occur under the conditions investigated.

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In comparison with other first-row transition metal catalyst/peroxide systems, this method works well for secondary alcohol oxidation, and some comparisons are noted in Tables S3 and S4.

**Table 1.** Oxidation of secondary aliphatic alcohols

Entry	Substrate	Conversion <sup>a</sup>	Yield <sup>a</sup>
1 <sup>b</sup>		48%	40%
2 <sup>c</sup>		86%	66%
3 <sup>b</sup>		80%	66%
3 <sup>c</sup>		96%	81%
4 <sup>b</sup>		82%	78%

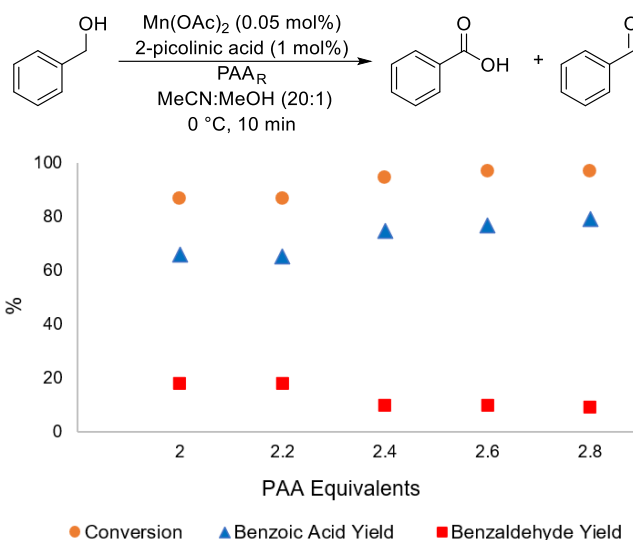
a. Conversion and yield by GC-FID, using benzonitrile as internal standard.

b. 1 mmol scale, 1 mL 2-picolinic acid (10 mM in MeCN) (1 mol%), 0.1 mL Mn(OAc)<sub>2</sub> (5 mM in MeOH) (0.05 mol%), 1 mL MeCN, 1.2 equiv PAAR added in 10 aliquots at 0 °C.

c. 1 mmol scale, 2 mL 2-picolinic acid (10 mM in MeCN) (2 mol%), 0.2 mL Mn(OAc)<sub>2</sub> (5 mM in MeOH) (0.1 mol%), 1 mL MeCN, 1.8 equiv PAAR added in 10 aliquots at 0 °C

### Primary Alcohol Oxidation

The direct conversion of a primary alcohol to a carboxylic acid is a useful synthetic transformation. This catalyst system is clearly strongly oxidizing and it is unlikely that a peroxide method such as this could produce the aldehyde selectively. Further development targeted optimization of the system to produce carboxylic acids with high selectivity. Initial investigations, shown in Figure 3, found that benzyl alcohol could be converted to benzoic acid in 77% yield using just 2.5 equivalents of peracetic acid. High selectivity for the acid over the aldehyde product was observed. The addition of further peracetic acid did not lead to improved results or result in complete conversion of aldehyde to carboxylic acid, indicating possible catalyst deactivation.



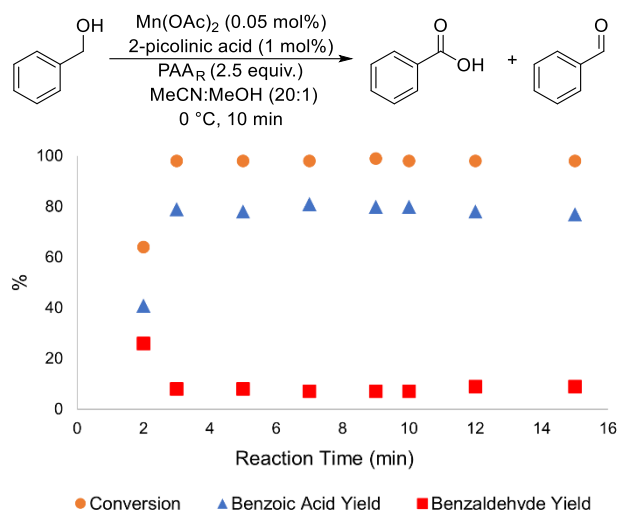
**Figure 3.** Benzyl alcohol oxidation with varying PAA equivalents. Conversion and yields determined by HPLC using benzophenone as internal standard.

A solvent screen was carried out (Table S5), showing that EtOAc could be employed in place of acetonitrile with little impact on results, whilst methanol led to lower conversion and yield. Since methanol is used as a co-solvent to prevent Mn(OAc)<sub>2</sub> precipitation, this raised concerns that this could be inhibiting the progress of the reaction. To investigate, reactions were carried out with Mn(OTf)<sub>2</sub>, as its solubility in acetonitrile allowed for the reaction to be conducted without the presence of methanol. The results showed a very slight increase in conversion and acid yield but was not sufficient to justify the use of the significantly more expensive triflate salt. A temperature screen was carried out (Figure S7), indicating that similar performance was obtained from -15 to 15 °C, but the reaction was significantly slower at -25 °C. This contrasted with the oxidation of secondary alcohols (Figure 1) and epoxidation of alkenes, suggesting the potential to carry out alkene epoxidation selectively in the presence of primary alcohol functionality (see later). Control reactions were carried out (Table S6) showing that all three components, metal, ligand and peracetic acid were required for this reaction to proceed.

The final conditions for primary alcohol substrates, as shown in Figure 4, indicating that the reaction reaches completion within 3 minutes, with no further reaction observed when the reaction time is extended to 15 minutes.

High yields of benzoic acid derivatives could be obtained from a broad range of benzylic alcohols with various substituents. Substrates with halogens Br, Cl and F in the para position (Table 2, Entries 2, 3 and 4) all showed excellent conversion with high selectivity for the acid product.

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**Figure 4.** Reaction profile for benzyl alcohol oxidation

In the case of the 4-iodo substrate (Table 2, Entry 9), the low conversion observed is likely due to the fact that peracetic acid can oxidize aryl iodides to their corresponding hypervalent iodine species.<sup>[55]</sup> It would appear that this competes with the catalytic alcohol oxidation and therefore this functionality is not suitable. Low reactivity was observed with the nitro substituted benzyl alcohol (Table 2, Entry 5), which is in contrast to a previous report by Browne and co-workers, which used a *N,N,N'*-trimethyl-1,4,7-triazacyclononane based Mn catalyst, along with salicylic acid and H<sub>2</sub>O<sub>2</sub>.<sup>[15]</sup> In this picolinic acid / PAA system, the nitro functionality appears to deactivate the catalyst, and this same behavior was observed with aldehyde oxidation (see later). 2-Phenylethanol (Table 2 Entry 13) was also tested as a substrate, with the crude <sup>1</sup>H NMR spectrum of the reaction mixture showing significant amounts of unreacted starting material. HPLC analysis to determine conversion and yield was not possible due to significant overlapping of peaks (2-phenylethanol, phenylacetaldehyde, phenylacetic acid and benzoic acid). GC-MS confirmed the presence of cleavage products, benzoic acid and benzaldehyde. Co-elution of benzoic acid and phenylacetic acid during isolation meant a 1.3:1 mixture of phenylacetic acid: benzoic acid was obtained rather than pure phenylacetic acid. The formation of cleavage products such as benzaldehyde and benzoic acid from 2-phenylethanol-like substrates has been previously reported.<sup>[15, 51]</sup>

**Table 2.** Oxidation of primary alcohols

Entry	Substrate <sup>a</sup>	Conversion <sup>b</sup>	Acid Yield <sup>b,c</sup>	Aldehyde Yield <sup>b</sup>
1		98%	80% (74%)	8%
2		98%	84% (67%)	4%
3		96%	73% (70%)	2%
4		98%	90% (81%)	1.5%
5		52%	25% (10%)	20%
6		100%	70% (61%)	3%
7		91%	30% (28%)	0%
8		98%	72% (63%)	1%
9		12%	1%	7%
10		97%	81%	16%
11		100%	80%	16%
12		100%	78%	1%
13 <sup>d</sup>			26 % Phenylacetic acid yield <sup>e,f</sup> 20 % Benzoic acid yield <sup>e,f</sup>	
14		62% <sup>g</sup>	(26%)	5% <sup>g</sup>

a. 1 mmol scale, 1 mL 2-picolinic acid (10mM in MeCN), 0.1 mL Mn(OAc)<sub>2</sub> (5 mM in MeOH), 1 mL MeCN, 2.5 equiv PAA<sub>R</sub> added in 10 aliquots at 0 °C.

b. Conversion and yield calculated using HPLC with benzophenone as internal standard c. Isolated yields in parenthesis d. Crude <sup>1</sup>H NMR of reaction mix showed ~1:1.2 ratio of 2-phenylethanol:phenylacetic acid

e. Isolated as a 1.3:1 mixture of phenylacetic acid: benzoic acid (<sup>1</sup>H NMR)

f. Overlapping peaks on HPLC prevented determination of HPLC conversion or yield. g. Determined by GC-FID using benzonitrile as an internal standard.

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Aliphatic substrates are known to be more challenging substrates, often demonstrating poor reactivity in oxidation systems. For example, some catalyst systems are limited to benzylic and allylic substrates.<sup>[56, 57]</sup> The aliphatic alcohol, 1-octanol, was tested under the developed conditions, demonstrating poor reactivity. This substrate afforded 62% conversion and a low isolated yield of 26% octanoic acid. Recovery may have been affected by product loss during isolation at the small scale. However, GC-MS analysis also indicated the formation of octyl octanoate, octyl acetate and methyl octanoate esters (see Figure S8). Octanal dimethyl acetal is another possible side-product observed by GC-MS analysis.

In agreement with previous observations with secondary alcohol substrates, the methoxy substituent (Entry 7) resulted in poor product selectivity. Figure S9 shows some potential by-products, suggested by GC-MS analysis of the reaction mixtures from 4-methoxybenzyl alcohol. Table S7 compares some other catalytic methods for some of the primary alcohols examined, further demonstrating that the methoxy group is challenging for other catalyst systems also.

### Aldehyde Oxidation

The oxidation of alcohols to carboxylic acids, proceeds *via* the corresponding aldehyde, therefore the oxidation of some aldehydes to carboxylic acids was examined. Aldehydes may be prepared *via* synthetic strategies other than alcohol oxidation (e.g. hydroformylation of alkenes), which suggests this is also a viable route for the synthesis of carboxylic acids.<sup>[58]</sup> As shown in Table S8, good conversion of the aldehyde to carboxylic acid could be achieved with 1 equivalent of PAA. Again, the 4-methoxy substituent resulted in comparatively low selectivity, indicating that the competing ester formation between aldehyde and alcohol substrate is not the major source of lower selectivity for the acid product previously observed in direct primary alcohol oxidation. The 4-nitro and 4-iodo benzaldehydes had relatively low conversion, which was also in-line with observations for the primary alcohols. Kappe and co-workers recently reported the oxidation of aldehydes in a continuous flow system using performic acid that was formed *in-situ*.<sup>[58]</sup> In this case, a catalyst was not required, and the performic acid could oxidize aldehydes to carboxylic acids at temperatures of 80 to 110 °C. The unstable nature of performic acid would prohibit the scaling of this reaction in a batch reactor. However, the utilization of a continuous flow system enabled the safety hazards to be circumvented. For the system described herein, it was found that the catalyst components were required when carrying out aldehyde oxidation at 0 °C, in control experiments (Table S9). It is also worth noting that in the Kappe catalyst-free system, 4-methoxy benzaldehyde was also a challenging substrate with the carboxylic acid product obtained in 35% yield.<sup>[58]</sup>

### Chemoselectivity

Intermolecular competition reactions were performed as shown in Table 3. These studies demonstrated that this system oxidizes secondary alcohols faster than primary alcohols. In the case of alkene epoxidation, this occurs selectively over both alcohol

substrates. This is in good agreement with previous competition experiments using similar systems conducted by both Moretti *et al.*<sup>[33]</sup> and Dong *et al.*<sup>[23]</sup> Using lower temperatures increases the selectivity, allowing for alkene epoxidation to be carried out with increased selectivity even in the presence of alcohol substrates.

**Table 3.** Intermolecular competition experiments

Entry	Temperature	Substrates	Conversion
1 <sup>a,b</sup>	0 °C	1-Phenylethanol	34%
		1-Octene	66%
2 <sup>a,b</sup>	-25 °C	1-Phenylethanol	23%
		1-Octene	71%
3 <sup>a,b,c</sup>	0 °C	1-Phenylethanol	39%
		Benzyl alcohol	32%
4 <sup>a,b,c</sup>	-25 °C	1-Phenylethanol	43%
		Benzyl alcohol	25%
5 <sup>a,b,c</sup>	0 °C	Benzyl alcohol	14%
		1-Octene	70%
6 <sup>a,b,c</sup>	-25 °C	Benzyl alcohol	7%
		1-Octene	80%

Reaction Conditions: 0.05 mol% Mn(OAc)<sub>2</sub> (5 mM in MeOH), 1 mol% 2-picolinic acid (10 mM in MeCN), 1 mL MeCN, 1.0 equiv. PAA<sub>R</sub> (added in 10 aliquots), 10 min. 1-Octene and 1-phenylethanol conversion measured using GC-FID with benzonitrile as internal standard. Benzyl alcohol conversion measured using HPLC with benzophenone as internal standard

Achieving very high selectivity for competing functional groups will always be challenging for such peroxide mediated systems, as these catalysts are normally highly reactive. Though we have not conducted any mechanistic investigations, there have been a number of particularly relevant studies worth highlighting here. Moretti studied Mn(II)/2-picolinic acid with PAA for alkene epoxidation.<sup>[37]</sup> From experimental and computational studies, they concluded that the active oxidant was likely [L<sub>2</sub>Mn<sup>IV</sup>-OOAc]<sup>+</sup>, a cationic Mn<sup>IV</sup>-peracetate complex. Recently, Kim *et al.* studied Mn(II)/2-picolinic acid with PAA for the oxidation of micropollutants in wastewater, and believed that the active oxidant was a high valent Mn<sup>V</sup> species.<sup>[38]</sup> Browne and co-workers have carried out in-depth mechanistic studies of Mn(II)/2-picolinic acid with H<sub>2</sub>O<sub>2</sub> and butanedione related to the oxidation of alkenes, alkanes and alcohols.<sup>[39, 40]</sup> Their studies find that H<sub>2</sub>O<sub>2</sub> and butanedione forms 3-hydroperoxy-3-hydroxybutanone which then reacts with the initial Mn<sup>II</sup> species to form a Mn<sup>III</sup> intermediate. This then leads to a highly reactive [Mn<sup>V</sup>(O)(OH)] or [Mn<sup>V</sup>(O)<sub>2</sub>] species. This high valent species can oxidize alkenes, alkanes, alcohols, butanedione and also leads to the disproportionation of H<sub>2</sub>O<sub>2</sub>.

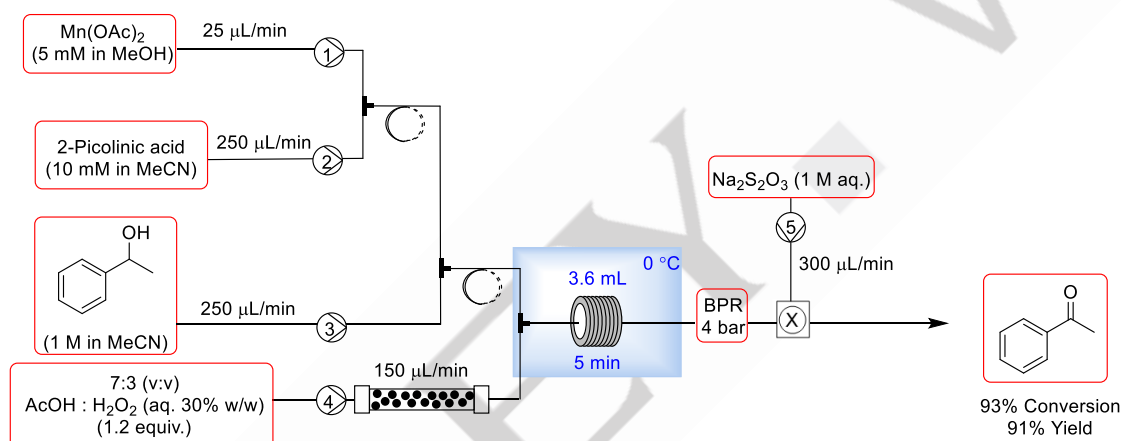
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## Continuous Flow Systems

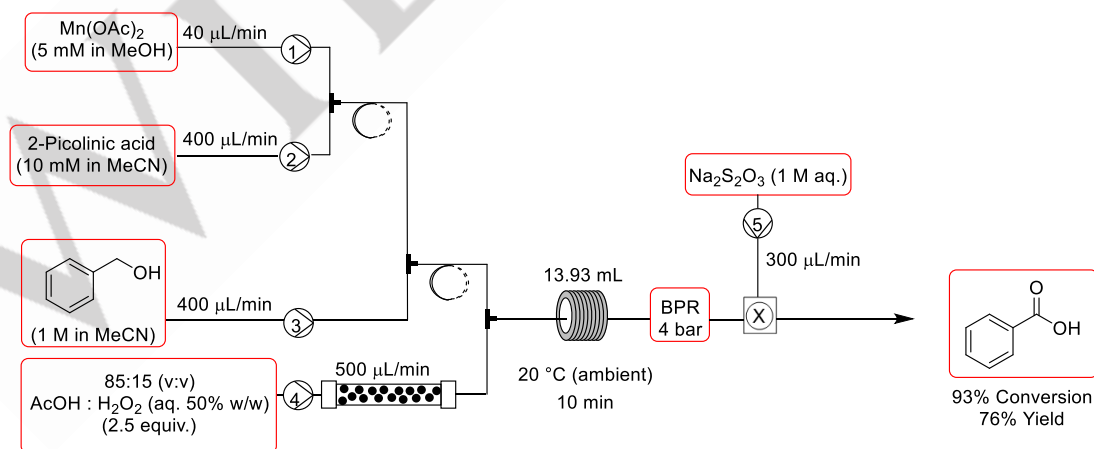
A key target was to demonstrate that these reactions could be performed in a continuous manner, enabling a safer, more scalable approach. Optimization studies were carried out in flow (S10 & S11 for 1-phenylethanol and S12 and S13 for benzyl alcohol). Figures 5 and 6 illustrate the final flow systems developed for 1-phenyl ethanol and benzyl alcohol. A picture of the flow set-up is also shown in Figure S14.

The systems shown use the inexpensive  $\text{Mn}(\text{OAc})_2$  salt forming the ligated complex *in-situ*, as this avoids precipitation of solids, which can result in blockages.<sup>[41]</sup> The peracetic acid was also produced *in-situ*, passing  $\text{H}_2\text{O}_2$  and acetic acid over a solid acid resin catalyst. Continuous operation of the flow system was maintained for 5 hours with no evidence of solids or reactor fouling observed. The conversions and yields were consistent across this time, and comparable to what had been obtained in batch

reactions, demonstrating the scalability of these reactions. An in-line quench was employed using a single fReactor unit. The fReactor unit is a stirred vessel with continuous input (reaction mixture and an aqueous solution of  $\text{Na}_2\text{S}_2\text{O}_3$ ) and output (quenched reaction mixture). The catalytic method does not require a large excess of PAA, but carrying out the quench in flow is desirable to avoid accumulation. Conducting the reduction of PAA in a continuous manner is significantly safer and more scalable. To confirm that all peroxides were quenched, potassium iodide was added to the collection flask, with no iodine colour observed. The conversion and yields obtained in the flow systems were consistent across the 5 h of operation. They are also in good agreement with the batch studies and illustrate that continuous flow approaches are suitable for reactions of this type.



**Figure 5.** Continuous flow system for 1-phenylethanol oxidation with the  $\text{Mn}(\text{OAc})_2$  (0.05 mol%) / 2-picolonic acid catalyst (1 mol%) and *in-situ* synthesis of peracetic acid.



**Figure 6.** Continuous flow system for benzyl alcohol oxidation with the  $\text{Mn}(\text{OAc})_2$  (0.05 mol%) / 2-picolonic acid (1 mol%) catalyst and *in-situ* synthesis of peracetic acid.

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## Conclusions

A manganese(II)/picolinic acid catalyst system was shown to be versatile and applicable for the oxidation of secondary alcohols to ketones and primary alcohols (or aldehydes) to carboxylic acids. The performance of the catalyst in terms of substrate scope and catalyst loadings is compares well to other peroxide-based systems. An attractive feature of this catalyst is that it uses an inexpensive commercially available ligand and manganese salt and the active catalyst is easily formed *in situ*. This makes the catalyst readily accessible suitable for larger scale applications. The rapid reaction kinetics and exothermic nature of the reactions studied result in good compatibility with continuous flow approaches for scale up.

## Supporting Information

Additional data and experimental details are given in the Supporting Information. Additional references also cited within the Supporting Information.<sup>[59-64]</sup>

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**Keywords:** Continuous flow • oxidation • peroxide • manganese • carbonyls

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The use of Mn(OAc)<sub>2</sub> and 2-picolinic acid was studied for the catalytic oxidation of alcohols. Low loadings of this inexpensive catalyst could be employed for these reactions, which uses peracetic acid as the oxidant. Reactions were fast and it was possible to move from batch conditions to continuous flow operation, which offers improved safety and scalability for such reactions.